AD_____
(Leave blank)

Award Number: W81XWH-08-2-0652

TITLE: *A Double Blind Trial of Divalproex Sodium for Affective Lability and Alcohol Use Following Traumatic Brain Injury*

PRINCIPAL INVESTIGATOR: Thomas P. Beresford, M.D.

CONTRACTING ORGANIZATION: Denver Research Institute
Denver, CO 80220

REPORT DATE: October 2013

TYPE OF REPORT: Addendum to Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
1 October 2013	Final Addendum	15 Sep 2012-14 Sep 2013

4. TITLE AND SUBTITLE
A Double Blind Trial of Divalproex Sodium for Affective Lability and Alcohol Use Following Traumatic Brain Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-2-0652

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Thomas P. Beresford, M.D.

EMAIL: thomas.beresford@ucdenver.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
.

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
A large and under-recognized sub-set of patients suffer from both traumatic brain injury (TBI) and alcohol abuse/dependence (AA/D). This group appears to use alcohol to self-treat fronto-limbic disinhibition, expressed clinically as affective lability, following TBI. This often results in AA/D and worsens TBI prognosis. The primary study hypothesis states that symptom frequencies of fronto-limbic disinhibition, expressed as affective lability, will decrease significantly in TBI subjects treated with divalproex sodium, a mood stabilizing medication, as compared to placebo. To test the primary hypothesis, we propose an 8 week, double-blind, randomized, controlled trial comparing divalproex sodium to placebo in 50 subjects—25 per group--who suffer from both TBI and AA/D. Subjects will be recruited through the initiating site located at the Department of Veterans Affairs Medical Center, Denver. Final approval from multiple review bodies was granted on September 15, 2009. Active subject recruitment continues. There are no results to report at this time.

15. SUBJECT TERMS- Traumatic Brain Injury, Alcohol Use, Mood, Mood Stabilization

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	10	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Introduction

Traumatic brain injury (TBI) is highly prevalent in at risk occupations including US service personnel. Of particular concern now are those wounded in combat in Iraq and Afghanistan where TBI appears to account for a larger proportion of casualties than in prior U.S. wars. Reports from Operation Iraqi Freedom (OIF) suggest that as many as one-quarter of personnel injured in combat there suffer TBI. (Okie, 2005) Psychiatric and neurocognitive disorders—especially disorders of mood--have been noted in as many as three-quarters of combatants who suffered TBI in previous conflicts (Lishman, 1973) and are often more adversely affected by emotional problems than by physical disabilities. (Nelson et al., 1998) Although specific data are not at hand, published frequencies suggest that as many as one combat related case of TBI in every five may likely exhibit symptoms related to fronto-limbic disinhibition that is expressed as a poorly controlled, or labile, affect. It is that condition that caught our clinical interest and led to a preliminary research project.

Specifically, the Principal Investigator (PI) observed a clinical population of former service personnel who served in high risk environments such as paratroop units, flight crews, and below decks aboard ship and who had suffered TBI. Common to all was a poorly managed affective irritability or anxiety that began after TBI and was often misdiagnosed as another Axis I psychiatric disorder, usually a mood disorder such as bipolar illness, or schizoaffective illness. Likewise, all of the cases had no such symptoms prior to TBI. This posed a clinical question: How to treat post-TBI affective lability/ fronto-limbic disinhibition?

As a class of agents, anticonvulsant medication appears, empirically, to lessen the affective lability in TBI. Carbamazepine may ameliorate agitation and disinhibited behavior as well as depression and manic symptoms following TBI. (Azouvi et al., 1999; Bakchine et al., 1989; Perino et al., 2001) Valproate may improve post-TBI aggressive behaviors (Wroblewski et al., 1997), episodic explosiveness (Geracioti, 1994), and bipolar syndrome. (Pope et al., 1988) Affective lability may include poorly controlled expression of mood and anxiety upset. (Arciniegas and Silver, 2001) Other agents, such as benzodiazepines may address similar symptoms, yet these drugs introduce addiction and tolerance issues and do not appear to address specific causes of affective lability.

To complicate matters clinically, the PI saw many cases in the veteran population in which TBI patients had been trying to self-treat their affectively lability—generally an irritability or anxiety state that interrupted or prevented normal functioning at work or in family life, often leading to broken marriages, job losses, occasionally to homelessness. Unfortunately, the most readily available drug of choice for many TBI victims was often ethyl alcohol. The result of self treatment was frequently the development of an alcohol use disorder that only served to worsen the fronto-limbic disinhibition following the TBI.

Alcohol abuse and/or dependence (AA/D) and mood disturbance often co-occur following TBI. (Corrigan, 1995) In a group of 20 TBI survivors who had evidence of alcohol abuse in the year following their injury, 15 (75%) developed a mood disorder. (Jorge and Robinson, 2002) In a non-alcohol abusing group, only 44% patients developed a mood disorder during the same time period. (Jorge and Robinson, 2002) In persons with AA/D and affective lability following TBI, successful treatment of mood lability may reduce or eliminate drinking behaviors.(Beresford et al., 2005) Following our interests in both alcoholism and TBI, we have accrued clinical experience in recognizing and treating patients who present with mood lability including symptoms of AA/D after TBI. We have observed a similar pattern of decrease in, or cessation of alcohol use following treatment of underlying TB I-induced affective lability. Many AA/D+TBI patients describe their emotional symptoms as contributing to their heavy alcohol

use. Observed clinically, when such cases reach alcohol abstinence, their symptoms of poorly regulated affective expression most often do not appear to be those of an idiopathic mood or anxiety disorder. They do not present the severity or the same natural courses as do Major Depressive Disorder, Bipolar Illness, or Anxiety Disorder, for example. Instead both symptoms and course appear more characteristic of the sustained affective lability often observed following TBI. (Beresford et al., 2005) This suggests that TBI survivors represent a patient group for whom treatment of neuropsychiatric symptoms following TBI may alleviate both TBI-related affective lability and also heavy ethanol use by treating the condition for which ethanol is used.

We believe our clinical observation of excessive alcohol use following TBI and the response to non-blinded, open-label treatment with anticonvulsant medications are concordant with the notion of neuronal inhibition, if noted in the absence of a clearly controlling mechanism of action. From a scientific viewpoint however, the treatment of fronto-limbic disinhibited patients has been neither blinded nor placebo-controlled to this point. As such, we can only provide an interesting observation of what appears to be a beneficial treatment response to anticonvulsant medication among patients with affective lability and AA/D following TBI. This indicates the need for a more systematic investigation of this phenomenon that, if substantiated, might improve the outcome and treatment choices for those patients who suffer from both TBI and AA/D. Further investigation requires us to focus on one agent for use in a soundly designed clinical trial. For this purpose, we have selected divalproex sodium.

Divalproex sodium is a standard and commonly used anticonvulsant and mood stabilizing agent that appears to be the best choice of active drug for the proposed study. It is a compound comprised of sodium valproate and valproic acid. In 1963, valproic acid was recognized to have anti-seizure activity, and it was approved as an anti-epileptic drug in the U.S. in 1978. The divalproex formulation, which is an enteric-coated, stable equimolar combination of sodium valproate and valproic acid, became available in 1983. In 1994, it was shown to be superior to placebo and comparable to lithium in treating acutely manic bipolar patients, and the FDA approved it in 1995 for this indication. Also, it is used in conjunction with lithium or carbamazepine to prevent recurrent manic or depressive episodes during long-term treatment of bipolar disorder (PDR, 2006).

This line of research opens an exciting area of inquiry that can 1) characterize a treatable clinical population more specifically than ever before and, 2) potentially offer an effective and widely available treatment modality that can ease the fronto-limbic disinhibition symptoms of TBI resulting in a significant lessening of ethanol intake for the same purpose. Because ethanol self-treatment often leads to increasing ethanol tolerance and the subsequent symptoms of AA/D, specific treatment for those suffering affective lability after TBI can potentially prevent AA/D in vulnerable individuals. In addition, specific treatment may also ameliorate AA/D in cases where it has already occurred. If found effective, anticonvulsant treatment for the mood and anxiety symptoms resulting from TBI offers the possibility of altering an otherwise downhill natural course into alcohol dependence, potentially affecting the many thousands of persons who suffer affective instability after closed head TBI. If proven, this treatment may act in both preventive and curative capacities. Last, establishing a treatment effect in this area will shed light on possible interactions between affective lability and neuro-inhibition as these relate to basic mechanisms whereby the brain's vulnerability to alcohol addiction becomes manifest. In short, if this study can demonstrate a valid effect it will open further doors of inquiry.

Body

Recruitment

This report closes the fifth year of study funding. As it took substantial time locally to receive all approvals for this project, we began enrollment near the end of the first year. For our initial efforts we targeted services and clinics at the Denver VA Medical Center (DVAMC) who regularly saw TBI patients. Dr. Beresford and Mr. Schmidt have made outreach presentations to the Substance Abuse Treatment Program (SATP), Mental Illness Research, Education and Clinical Center (MIRECC), Inpatient Psychiatry, Outpatient Mental Health Clinic, TBI Clinic personnel and others. We have continued generalized outreach, advertising the study throughout the DVAMC with flyers and brochures. We consented our first participant in October 2009. This was followed by the first subject to be randomized to the study drug trial in February 2010. Since then we have expanded our outreach beyond the DVAMC by running advertisements in local newspapers, public transit and more recently, television. The television ads provided a significant boost to recruitment and have propelled us to within three subjects of completion.

The past year has seen us enroll and randomize participants at a brisk pace. As of October 1st, 2013, we have randomized 47 patients into the drug trial (Figure 1) from a population of 595 potential candidates, of whom 96 were evaluated for study entry in person. We have collected usable data from all 47 subjects randomized and a total of 34 (72%) have completed the protocol. As this number remains below the recruitment goal of the study, we requested and were recently granted a second no-cost extension of one year to the original timeframe of the study.

Following the success of local television advertising for another of our medication trials, we decided to produce and air ads for this trial. As this form of advertising comes at a significant cost premium, we chose to run a four-day trial of ads. Working with our vender, television shows were chosen during daytime hours based on viewership demographics and a simple ad was produced and aired. This yielded a tremendous volume of calls, with our research assistants reporting that they screened 196 potential participants due the television ads. More critically, we were able to consent thirteen and randomize six new participants due to the television ads.

As the first ad run was such a success we opted to do additional advertising in the summer once the large cohort of participants from the first batch of ads had completed the trial. This similar ad run yielded an additional 74 phone contacts and nine additional consents. Of those consented we were able to randomize six.

In the past year we also hired two new research assistants to screen calls, promote the study and continue our outreach efforts. Having the additional personnel was critical in handling the heavy volume of inquiries and participants following our television ads. The additional personnel have also been instrumental in the absence of Mr. Schmidt due to the birth of his daughter in August. While our new staff have been able to meet the demands of the participants currently on the protocol, further recruitment of new subjects is slowed until Mr. Schmidt returns in October.

Reviewing our randomized subjects to this point, we are pleased that participant compliance continues to be remarkably high, with 72% (34/47) completing the protocol once randomized, well above the anticipated 50% dropout rate.

In the coming year we hope to recruit the final three participants for the study at a rapid pace to allow significant time for data analysis and manuscript preparation. Following the recruitment successes of the past year we are confident this is a reasonable goal.

Key Research Accomplishments

At this stage of the investigation the study continues to compile and store research data. According to study design we have not yet begun to analyze these data with respect to the study hypotheses. A blinded, mid-course data quality review was conducted after reaching the 50% of recruitment. Those data did not suggest an overwhelmingly positive or negative effect of the active drug, and indicated the need for accruing the original sample size. We anticipate elucidating principal research accomplishments once enrollment is complete, the study blind is broken and we analyze the data.

Reportable Outcomes

None at this time.

Conclusion

Any primary conclusions from the blinded study will occur after data collection and analysis have been completed and the study blind opened at that point. In the meantime we will continue to formulate and explore new questions and hypotheses from non-blinded data.

References

01. Okie, S. Traumatic brain injury in the war zone. *New England Journal Medicine 2005: 352:2043-2047.*
02. Lishman, WA. The psychiatric sequelae of head injury: a review. *Psychological Medicine 1973:3(3):304-18.*
03. Nelson LD, Drebing C, Satz P, Uchiyama C. Personality change in head trauma: a validity study of the Neuropsychology Behavior and Affect Profile. *Archives of Clinical Neuropsychology* 1998:**13**(6):549-60.
04. Azouvi P, Jokic C, Attal N, Denys P, Markabi S, Bussel B. Carbamazepine in agitation and aggressive behaviour following severe closed-head injury: results of an open trial. *Brain Injury* 1999;**13**(10)**:**797-804.
05. Bakchine S, Lacomblez L, Benoit N, Parisot D, Chain F, Lhermitte F. Manic-like state after bilateral orbitofrontal and right temporoparietal injury: efficacy of clonidine. *Neurology* 1989;**39**(6)**:**777-81.
06. Perino C, Rago R, Cicolini A, Torta R, Monaco F. Mood and behavioural disorders following traumatic brain injury: clinical evaluation and pharmacological management. *Brain Injury* 2001;**15**(2)**:**139-48.
07. Wroblewski BA, Joseph AB, Kupfer J, Kalliel K. Effectiveness of valproic acid on destructive and aggressive behaviours in patients with acquired brain injury. *Brain Injury* 1997;**11**(1)**:**37-47.
08. Geracioti TD, Jr. Valproic acid treatment of episodic explosiveness related to brain injury. *Journal of Clinical Psychiatry* 1994;**55**(9)**:**416-7.
09. Pope HG, Jr., McElroy SL, Satlin A, Hudson JI, Keck PE, Jr., Kalish R. Head injury, bipolar disorder, and response to valproate. *Comprehensive Psychiatry* 1988;**29**(1)**:**34-8.
10. Arciniegas DB, Silver JM. Regarding the search for a unified definition of mild traumatic brain injury. *Brain Injury* 2001;**15**(7)**:**649-52.
11. Corrigan JD. Substance abuse as a mediating factor in outcome from traumatic brain injury. *Archives of Physical Medicine & Rehabilitation.* 1995;**76**(4)**:**302-9.
12. Jorge R, Robinson RG. Mood disorders following traumatic brain injury. *NeuroRehabilitation* 2002;**17**(4):311-24.
13. Beresford TP, Arciniegas D, Clapp L, Martin B, Alfers J. Reduction of affective lability and alcohol use following traumatic brain injury: a clinical pilot study of anti-convulsant medications. *Brain Injury* 2005;**19**(4)**:**309-13.
14. *Physicians' Desk Reference.* 60th ed. Montvale, NJ: Thomson PDR, 2006.
15. Beresford, TP. Reduction of affective lability and alcohol use following traumatic brain injury: a clinical pilot study of anticonvulsant medications. Military Health Research Forum, August 31, 2009, Kansas City, MO.
16. Beresford TP, Arciniegas DB, Alfers J, Clapp L, Martin B, Du Y, Liu D, Shen D, Davatzikos C. Hippocampus volume loss due to chronic heavy drinking. *Alcohol Clin Exp Res.* 2006;**30**(11):1866-70.

Appendix

Figure 1:

Enrollment Log

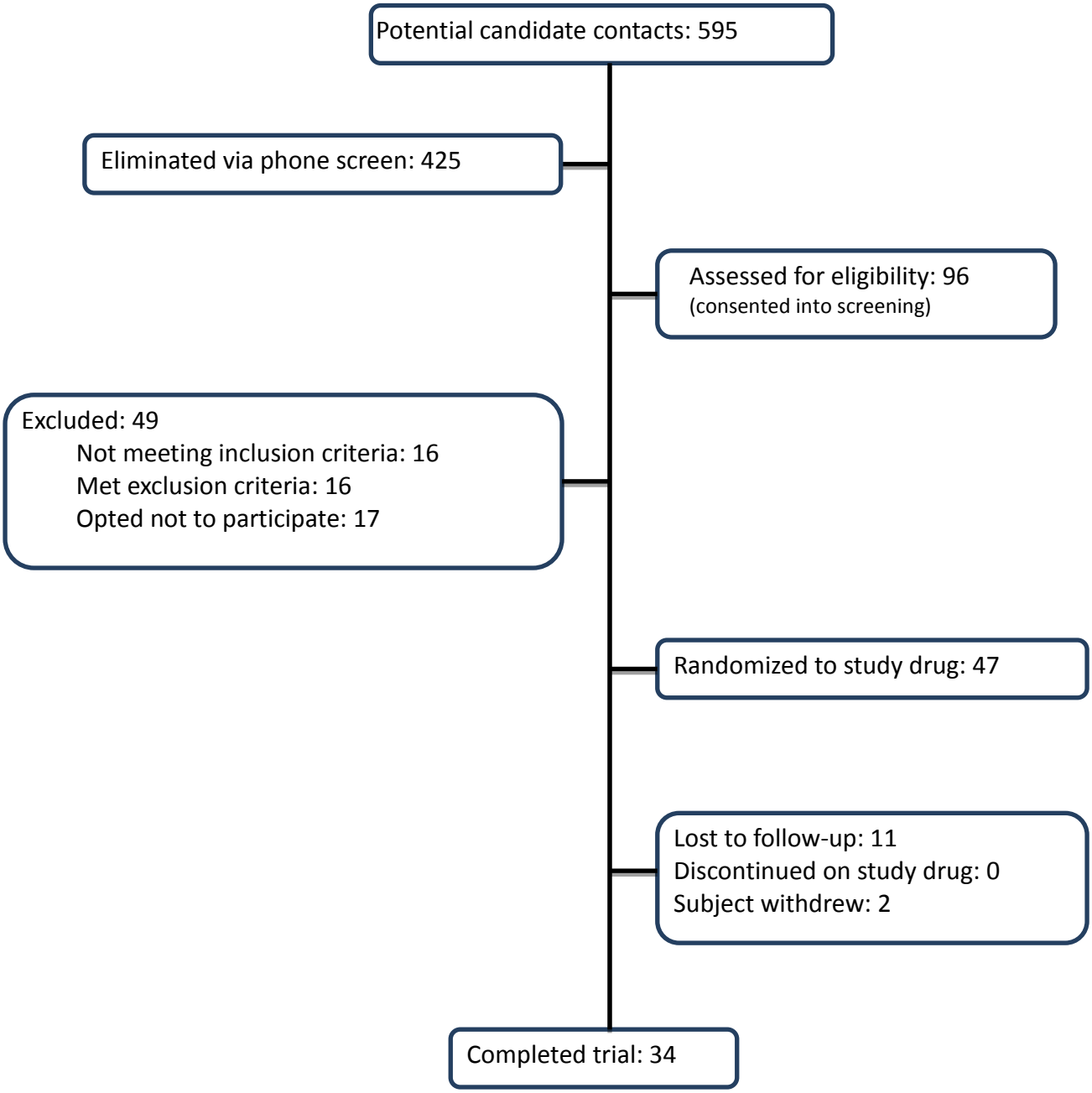

Figure 2:

Participants Randomized